INHERITED PREDISPOSITION FOR A BACTERIAL DISEASE

As soon as it can be demonstrated that in a process under investigation a given factor has a very marked influence, this factor is more often than not looked upon as the sole cause of what happens. It is indeed very difficult not to overemphasize the importance of a new link in a chain of causes, which has been hitherto overlooked, and which one is fortunate enough to discover. To give a few instances from a field familiar to us, we can cite three factors in the evolution of species which have each by one author been elevated to the rank of "the" cause of species formation. Natural selection was the cause of evolution in the eyes of Weismann, and every other factor was looked upon as subordinate. In the same way Wagner overemphasized the importance of isolation, and de Vries would have us believe that mutation was the main, if not the sole, cause of evolution. The greatness of Charles Darwin lies in the fact, that he was not led away from a consideration of all the possible factors by the temptation to pad out the importance of any one link in the chain of causes.

In a few instances the discovery of a new and very important factor in the causation of a process or set of phenomena sets all the investigators working in the new field just opened up. And often the attention is unduly taken away from other causes. In pathology the discovery of the rôle which microorganisms play in the causation of certain diseases has resulted in the almost absolute neglect of the study of possible other factors in the causation of these same diseases.

In the illness of an individual, infection by a specific microorganism is a very important factor in certain cases. But it is clear that, besides this infection, other factors influencing the qualities of the subject can be of great importance. Very often we find that, besides the presence of the specific organism, predisposing factors play an important rôle, such as the simultaneous presence of another infection (tuberculosis after measles) special conditions (diabetes, possibly beri-beri); causes lowering the vitality (exhaustion, inanition).

Besides factors of the environment, which in themselves are not pathogenic factors, it is evident that factors given in the composition of the individual, inherited factors, can cooperate in the causation of disease.

To make the statement general, we can say that illness is a condition caused by the cooperation of a series of factors, of which some are genetic, heritable, given in the composition of the individual's germ, and others are non-genetic, influencing the individual from the outside. In different combinations of other causes, individual factors can have a very different influence. In certain cases, therefore, different factors can be looked upon as the one which tips the scale, and consequently as "the" pathogenic moment.

The discovery of microorganisms and their rôle in disease has relegated other pathogenic causes to the background, and especially in those diseases where presence of the specific microorganism can always be demonstrated.

In some diseases the presence of a specific microorganism is not demonstrated, and an important non-bacterial factor seems to be the chief determining cause (some cases of carcinoma and of traumatic diabetes). In other cases, presence of a specific microorganism is certain demonstrable, but it seems as if other factors play an important rôle. Tuberculosis is a typical instance. And finally we know diseases, in which it appears as if presence or absence of a specific microorganism constitutes the almost exclusive cause of the difference between affected and healthy individuals (plague).

In the first group, diseases in which microorganisms play no rôle, the factors which cause the abnormal condition can be real environmental factors, but in some instances they are clearly genetic factors, developmental factors transmitted through the germ, genes. We know real hereditary diseases, where an inherited, genotypic peculiarity seems to be the causating factor (hemophily, Huntington's chorea, Daltonism).

In the second group, in those cases, therefore, where predisposition seems to have an influence comparable in its magnitude to infection, this predisposition can have very different causes. In some cases the cause of a predisposition is very clearly non-genetic, environmental (pneumonia after influenza, tuberculosis of the joints after trauma). In other cases, however, inherited constitution is very probably an important factor.

The "inheritance" of tuberculosis has been a point of unending controversy. Very often tuberculosis occurs in families in a way which makes us think of inheritance. According to many authors this occurrence of tuberculosis in families is simply caused by the greatly enhanced chances for a heavy infection. Others

however believe in the possibility of a real inheritance of the disease. It is very evident that the discussion has been very much hampered by a confusion of "inherited" and "congenital." And it has seemed to a great many authorities as if the question as to the existence of an inherited moment in tuberculosis could be answered by an investigation into the possibility of pre-natal infection.

Lastly, there are authors who believe in the inheritance of a certain disposition for tuberculosis.

From the fact that practically all persons above the age of twelve react positively to von Pirquet's test, it can be seen that tuberculosis infection is not as inevitably the cause of tuberculosis, as for instance pneumococcus infection is the cause of septicæmia in the mouse. Every practising physician has seen cases in which a joint became tuberculous after a trauma, in a patient who showed no other evidence of a tuberculous infection. But the fact that such cases are rare makes it probable that constitutional, genetic, differences in resistance exist between individuals. The same holds true for traumatic carcinoma.

It is evident that the study of the inheritance of constitutional predisposition to a disease must be almost impossible, where infection is so general as in the case of tuberculosis. We can only hope to find instances of the inheritance of predisposition or reversely, of immunity to a bacterial disease in cases where we are dealing with one, or with very few genetic factors, genes, whose influence on the resistance happens to be very marked indeed.

Now, in principle, there are reasons to believe in the possibility of an inheritance of immunity or predisposition for bacterial diseases. In the first place we have those instances, in which closely related varieties or species differ in resistance to a specific bacterial infection. A classical instance is that of the Algerian sheep, which are constitutionally immune to anthrax.

Another, similar instance was met by us in our work with rats. We found that there was a striking lack of uniformity in the practical results of the use of a paratyphus culture as distributed by the State Serum-institute of Holland for exterminating rats. In some parts of Holland the broth-culture was highly effective and very well spoken of, whereas it was almost wholly ineffective in other provinces. It appeared to us that this difference might depend upon the species of rats against which the culture was used. It was discovered by some joint work of the Koloniaal

Instituut and ourselves, that the Norway rat, which is the common rat in most parts of Holland, was practically, if not wholly, absent from parts of Friesland. In these parts *Mus rattus* is the common rat. Whereas *Mus norvegicus* succumbs readily to an ingestion of the broth culture as prepared by the Institute, we found the *Mus rattus* animals immune. Before we started for Java, we tried the pathogenic influence of the culture as furnished to farmers, on some of our cultivated rats of the *Mus rattus* group, on request of our ministry of colonial affairs. The rats were fed on a broth culture of a virulent strain of paratyphoid and bread, at the Serum-institute, and they remained in good health on this diet. The same culture killed practically all *Mus norvegicus* rats in a few days.

To our great regret we have never yet succeeded in obtaining hybrids between the two groups of rats, *norvegicus* and *rattus,* and for this reason the inheritance of this very marked immunity of *Mus rattus,* or in other words predisposition of *Mus norvegicus* can not be studied. We know of no case in the literature, of an investigation of the inheritance of immunity to bacterial disease in animals.

As is well known, Biffen found a case of the inheritance of resistance to rust in wheat, in which the difference between immune and easily infected plants was proved to be due to presence or absence of one single gene. William Orton and Webber have since found almost similar instances in cotton and watermelons.

So far as known to the authors, the following case of the inheritance of immunity, or predisposition for a microbial disease in animals is the first one studied so far.

From Nagasaki, Japan, and Hong Kong, China, we brought along some stock of a very minute domestic mouse. These mice evidently belong to the same group as the commonly imported oriental Waltzing mice. As a matter of fact, our Japanese animals of the second importation produced some waltzing offspring. We used this material for a few series of experiments on the inheritance of weight, one series starting from the only fertile Hong Kong female, and the others from diverse combinations of the Nagasaki strain with large white mice. These white mice are of a pure-bred strain used by T. B. Robertson in his experiments on growth. We produced numerous hybrids, great numbers of F_2 animals, and further we are grading back the hybrids both to the dwarf and to the heavy strain. For our work individual

mice are frequently weighed, and from time to time the whole series is weighed.

In the beginning of January an epidemic started in our mousery. Our mice were at that time housed in approximately seven hundred cages containing several thousand mice, both the size-inheritance and other series of breeding experiments. The cages of all the series were mixed and arranged on shelves in three adjacent rooms. The infection apparently swept through the entire colony, notwithstanding our attempts to limit it to one room. The Japanese mice were distributed over all the stacks in all three rooms, most of them mated to big mice or hybrids of different generations. All these mice fell victim to the epidemic, excepting three which we kept for a little while longer, by taking them into the living house at the beginning of the trouble. To our surprise the white mice of Robertson's strain proved immune. Even where the dead Japanese were partially eaten by their mates, these latter remained in good health.

It is clear that the main circumstance, which made it possible for us to see the clearcut segregation about to be described, was the rapid spread of the epidemic. All the Japanese mice were dead before the virulence of the microorganism was materially altered.

The rapid course of the disease made it possible to distinguish simply between dead and surviving mice. As a rule we found that animals contracting the disease presented the bunched up appearance and walked with the small, prancing steps familiar to students of paratyphoid in small rodents. They would be visibly ill for one, two, or exceptionally three days before death. We do not remember having seen one recover.

Professor Hall, of the department of bacteriology, of the University of California, was kind enough to make a bacteriological examination of the dying animals, and was able to isolate the same staphylococcus from the blood of the heart of four animals.

If we count the proportion of the animals which succumbed to the epidemic, we have to limit our countings to groups which are comparable. Immunity can never be anything but relative, and if we want simply to use the fact of survival as a criterion for immunity we must exclude as far as possible other causes of death. Of these the two main causes are death or illness of the mother, causing starvation of the young, and troubles in parturition.

In our study of the inheritance of immunity to this staphylo-

coccus infection we have therefore limited our counts to animals of the same age-group, that is to mice of at least four weeks old and not yet used for breeding.

At the general weighing of January 4, 1919, no losses were observed among the Japanese mice. Shortly afterward the Japanese started to die off. And at the general weighing of February 14, the last Japanese mouse was found dead.

The data given in this paper are taken from the records of this general weighing of February 14, 1919. They include litters of six kinds, pure Japanese, pure Robertson's whites, F_1 hybrids, F_2 hybrids, mice with one parent F_1 and the other Japanese, and such with one parent F_1 and one large parent.

As noted above all the Japanese left in the mousery died between January 4 and February 14, 59 in all. Of these 23 were in the class of weaned young, not yet breeding.

TABLE I

Litters of F_2 Animals Jan 4	Same Litters on Febr. 14	Litters of F_2 Animals Jan 4	Same Litters on Febr. 14
7	4	1	1
3	2	3	3
6	6	3	3
2	2	6	2
6	6	2	2
5	2	5	4
5	4	4	4
4	3	3	2
2	2	1	1
3	3	3	1
4	3	6	5
5	4	7	6
6	3	3	3
6	4	2	2
3	1	4	0
5	3	Total 125	91

As to the Robertson large strain, no deaths were observed within this period of six weeks among mice of this age class. A very considerable number of these weaned young were growing up in cages together with Japanese of their age and sex.

Between January 4 and February 14 we lost no F_1 animals after weaning age. Strictly comparable to the other lots were only three litters, which were weaned within the critical six weeks and not yet put to breeding. These litters contained fourteen young. All were living on February 14.

This shows how the immunity to this staphylococcus disease of the large albino strain as opposed to the predisposition to it of the Japanese strain, is completely dominant in the hybrids.

To our great surprise we found that this difference between immunity and predisposition was caused by presence or absence of one single genetic factor. In other words, we found a very clear monofactorial Mendelian segregation in F_2. As we are weighing non-breeding F_2 animals up to a relatively high age, thirty-one litters containing 125 animals fell into this class between the two dates.

Of these 125 animals 91 were living on February 14, and 34 had died. (Theoretical expectation 93.75 : 31.25.) See Table I.

If in reality the "Robertson" mice have one gene, lacking in the Japanese, whose presence protects them against death from this infection, we would expect the hybrids to produce 50 per cent. gametes with and as many without this gene. As the Japanese lack this gene, we would expect 50 per cent. of the young from matings between F_1 and Japanese to be immune, and 50 per cent. to die. Fourteen such litters were available for the test, with 57 animals. Of these 57 on February 14, there were 25 left, 32 having died. (Theoretical expectation equality.) See Table II.

TABLE II

Litters of F_1 × Japanese on Jan. 4	Same Litters on Febr. 14	Litters of F_1 × Japanese on Jan. 4	Same Litters on Febr. 14
6	3	2	2
7	1	2	1
3	1	5	1
5	5	3	0
4	4	5	1
6	4	5	0
2	2	2	0
		Total 57	25

In the same class with the other litters we had sixteen litters of young, each from one F_1 and one "Robertson" parent. This gave us 51 mice in this class. Fifty of these were living February 14, one having died. (Theoretical expectation no deaths.)

As will be seen in nearly every case the number of deaths was slightly greater than expectation. Occasional mice will die even when given the best of care. It is indeed remarkable that not more of these vigorous mice, kept for the most part in company with several of their own sex, got killed fighting. It must

be remembered that these figures for deaths comprise all cases of absence. Mice killed in fights and animals escaped are classed as dead.

The numbers published in this note were collected only after the epidemic had done its worst, and from our weighing records. The epidemic seriously interfered with some of our planned series in our breeding work on weight.

It was planned to start a series of infection-experiments with the isolated staphylococcus strains on families of F_2 animals. It may be possible at some future date to do this, when the material will again be in the right condition for the experiment, that is to say, free of spontaneous infection. At present, however, it is evident that the staphylococcus infection is still in our mousery. The mortality in F_2 families remains high. It is clear that, if we subjected F_2 animals to infection with a pure culture of the staphylococcus, the group of animals would be already a selected group, and the results would be quite misleading.

We have refrained from publishing these data for some time, hoping that we could free our mousery from the infection, so that we could repeat under conditions of a laboratory experiment the immunity tests of F_2 families. There seems no further reason now to withhold the facts such as they are.

As far as we are aware no wholly comparable instance is known so far of a gene whose action has such a definite effect upon the resistance to a bacterial disease in animals. The evidence for the inheritance of a differential susceptibility to transplanted tumors in Japanese and large mice in the work of Tyzzer is scarcely as definite as our case.

In any case, this instance recorded here proves clearly that the presence of a definite pathogenic organism as a factor in a transmittable disease need not be the sole determining cause of the disease. And it shows that the search for heritable factors in the causation of bacterial diseases is neither hopeless nor unscientific. We can only hope that cases such as the one just given will encourage those medical investigators who believe that predisposition is a factor not to be lost sight of in the press of bacteriological and related discoveries.

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NOTE ON THE PHOTIC SENSITIVITY OF THE CHITONS[1]

1. The remarkable sensory organs discovered by Mosely (1885) in the tegmentum of the shell-valves of certain chitons are structurally of such a nature that in their most highly developed forms they were from the first recognized to be "eyes." Practically nothing has been made known as to the functional values of these organs, which in different genera occur in a great diversity of form, number, and arrangement. It has been shown, however, that the tegmental æsthetes of *Chiton tuberculatus* are indeed photosensitive (Arey and Crozier, 1919). But the shell-eyes are in this genus generally represented by structures of an intermediate degree of complexity. The "eyes" are supposed to have been derived from large, relatively undifferentiated shell receptors (macræsthetes), and seem to reach their highest development in those species of *Schizochiton* and *Tonica* which possess large complex eyes, each surrounded by a pigment cup (*cf.* Plate, 1899; Nowikoff, 1907, 1909); in *Chiton* (at least in some species of this genus) the eyes are "*intrapigmental,*" pigment being contained within the receptor cells, whereas with the "*extrapigmental*" eyes the associated pigment occurs outside

[1] Contributions from the Bermuda Biological Station for Research.